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Arctigenin attenuates inflammation in vitro and in vivo by inhibiting the PI3K/AKT pathway and polarizing M1 macrophages towards M2-like macrophages - Review of the evidence

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1. ABSTRACT

The analyzed publication evaluated whether arctigenin, a natural substance found in the seeds of *Arctium lappa*, can reduce inflammation in macrophages and mouse models. In macrophages stimulated with lipopolysaccharide, a bacterial component used to trigger an experimental inflammatory response, the compound reduced the expression of IL-1b, IL-6, and TNF-a and increased IL-10 and CD204. In parallel, it reduced the phosphorylation—that is, the functional activation—of PI3K, AKT, and IKKb. In mice, arctigenin reduced certain measures of systemic inflammation and experimentally induced colitis.In section 6.4 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the study contributes to the narrative that arctigenin reduces pro-inflammatory cytokines in macrophages and promotes M2-like characteristics through the inhibition of the PI3K/AKT pathway. Independent studies in cells and mice have observed, in selected inflammatory contexts, a reduction in PI3K/AKT/mTOR signals associated with lower M1 polarization and/or higher M2 markers. However, other research shows that the activation of PI3K, AKT, and mTOR may be necessary for IL-4-induced M2 polarization. The most prudent conclusion is therefore mechanistic: the result is consistent with a reduction of pro-inflammatory activation in specific models, but it does not demonstrate a universal effect of PI3K/AKT inhibition on macrophage polarization in humans.

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2. ANALYZED STUDY

The research question was whether arctigenin could attenuate an experimental inflammatory response and through which cellular signals. The hypothesis evaluated was that the compound would reduce the activation of macrophages, immune cells that can produce mediators of inflammation, by acting on the PI3K/AKT pathway. PI3K and AKT are proteins that transmit signals within the cell and, depending on the stimulus and cell type, can contribute to different responses.The relevance to paragraph 6.4 is precise: the analyzed study documents a reduction in the cytokines IL-1b, IL-6, and TNF-a in macrophages, accompanied by an increase in IL-10 and CD204, and a reduction in the activation of PI3K and AKT. These results support the cellular segment of the narrative, not a clinical demonstration of therapeutic efficacy in human autoimmune or inflammatory diseases.Since the only available material is the abstract, it is not possible to reconstruct all experimental details or numerically verify the magnitude of the effects. The study allows for the description of experimental associations in cells and mice; it does not allow for the establishment of safety, effective doses, or benefits in humans.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The study included *in vitro* experiments on peritoneal macrophages, i.e., macrophages obtained from the abdominal cavity of animals, stimulated with lipopolysaccharide (LPS), a component of the cell wall of certain bacteria that triggers an inflammatory response. The authors evaluated the expression of pro-inflammatory cytokines, including IL-1b, IL-6, and TNF-a, and molecules associated with a more regulatory response, IL-10 and CD204.To clarify the possible mechanism, the phosphorylation of PI3K, AKT, IKKb, and IRAK-1—proteins involved in the transmission of inflammatory signals—and the activation of NF-kB, a factor that promotes the transcription of many inflammation genes, were examined. Silencing via small interfering RNA or siRNA, a technique that reduces the expression of a specific gene, was also used, targeting PI3K.The *in vivo* experiments included mice with systemic inflammation induced by intraperitoneal injection of LPS and mice with colitis induced by TNBS, a substance used to provoke experimental colon inflammation. Blood levels of cytokines, colon shortening, macroscopic scores, and myeloperoxidase activity—an enzyme used as an indirect indicator of inflammatory cell infiltration—were considered. The number of animals, sex, strain, doses, treatment times, randomization criteria, blinding of assessments, statistical analyses, and numerical values are not reported in the available material.

4. RESULTS

In LPS-stimulated macrophages, arctigenin reduced the increased expression of IL-1b, IL-6, and TNF-a. In simple terms, it attenuated three signals that help amplify the inflammatory response. In the same cells, it increased IL-10 and CD204, two markers consistent with a more regulatory or M2-like profile. The abstract does not report absolute values, percentage changes, concentrations, sample sizes, or statistical significance values.At the molecular level, arctigenin reduced the LPS-induced phosphorylation of PI3K, AKT, and IKKb, but not that of IRAK-1. It also reduced the translocation of NF-kB p65 into the nucleus, a necessary step for this factor to regulate numerous inflammation genes. In experiments using siRNA against PI3K, arctigenin did not further inhibit LPS-induced NF-kB activation. This finding is consistent with the involvement of PI3K in the portion of the cascade on which the compound acts, but it does not prove that PI3K is the sole target of arctigenin.In mice with LPS-induced systemic inflammation, arctigenin reduced blood levels of IL-1b and TNF-a. In the TNBS-induced colitis model, it reduced colon shortening, macroscopic scores, and myeloperoxidase activity. It also reduced IL-1b, TNF-a, IL-6, the phosphorylation of PI3K, AKT, and IKKb, and the activation of NF-kB; conversely, it increased IL-10 and CD204. For these results as well, the available material does not report effect sizes, confidence intervals, or P-values.

5. INTERPRETATION

The main significance is that, in this experimental system, arctigenin was associated with lower production of pro-inflammatory signals and higher levels of two markers linked to a more regulatory macrophage profile. The proposed biological

sequence is: reduced activation of PI3K and AKT, lower activation of IKKb and NF-kB, and lower expression of inflammatory cytokines.The specific finding supporting the book's paragraph is the simultaneous reduction of IL-1b, IL-6, and TNF-a and the increase of IL-10 and CD204 in macrophages, observed alongside the decrease in PI3K and AKT phosphorylation. Defining this result as a complete polarization from M1 to M2 requires caution: IL-10 and CD204 are informative markers, but the abstract does not describe a complete panel of markers, cellular functions, or cell fate tracking
experiments.Furthermore, M1 and M2 are useful categories for describing extremes of activation in the laboratory, whereas in real tissues, macrophages can assume intermediate and changing states. The data in mice reinforce the biological consistency of the result, but they do not prove that arctigenin prevents or treats colitis, autoimmunity, or other pathologies in humans.

6. INDEPENDENT SUPPORTING EVIDENCE

Confirmation that closely aligns with the narrative in this section comes from a study on LZ205, a flavonoid distinct from arctigenin. In macrophages and in mice with dextran sulfate sodium-induced colitis or alum-induced peritonitis, LZ205 reduced M1 polarization and the secretion of pro-inflammatory cytokines; in tissues and macrophages, it also reduced the expression or activation of PI3K, AKT, and mTOR. This research directly confirms, albeit only experimentally, that in certain inflammatory models, the reduction of this cascade can be accompanied by fewer M1 characteristics and less inflammation. It does not demonstrate that any PI3K/AKT inhibitor necessarily promotes the M2 state, nor does it provide clinical evidence [1].A second study analyzed exosomes, small vesicles released by cells, obtained from mesenchymal stem cells preconditioned with LPS. In macrophages exposed to inflammation, these exosomes increased M2 polarization and reduced M1 markers; the proposed mechanism involved microRNA-150-5p, the reduction of Irs1, and lower activation of the PI3K/AKT/mTOR pathway. In a mouse model of sepsis, the exosomes reduced pro-inflammatory cytokines, organ damage, and mortality compared to non-preconditioned exosomes. This is an independent mechanistic confirmation of the direction described in the book, but it concerns a complex intervention and not arctigenin [2].A third study identified a control circuit for pro-inflammatory macrophages in which the SIRPa-SHP-1 signal markedly inhibits PI3K-Akt2. In macrophages subjected to M1 stimuli, this inhibition attenuated the production of pro-inflammatory cytokines and the expression of programs associated with antigen presentation; in mouse models, the loss of this brake aggravated inflammation. The work does not demonstrate a complete conversion toward M2, but it confirms the most solid segment of the chain for this section: lower PI3K/Akt2 activity can reduce pro-inflammatory activation in a defined context [3].Taken together, these studies primarily support the link between the selective reduction of the PI3K/AKT signal and the attenuation of pro-inflammatory macrophage programs. The confirmation remains predominantly cellular and animal-based. None of these works demonstrate that arctigenin is an effective or safe treatment for people with inflammatory diseases.

7. CONFLICTING EVIDENCE

Directly relevant evidence suggests that the relationship between PI3K/AKT/mTOR and M2 polarization should not be considered linear. In mouse bone marrow-derived macrophages, Kimura and colleagues observed that Lamtor1, a protein that enables mTORC1 activation in response to amino acids and IL-4, is necessary for efficient M2 polarization. Lamtor1 deficiency, amino acid deprivation, or mTOR inhibition reduced M2 markers and increased M1 characteristics [4].This result does not negate the data from the analyzed study, because the models and stimuli are different: arctigenin was studied primarily during LPS activation, while the conflicting study examined alternative polarization induced by IL-4 and nutritional signals. However, it shows that the inhibition of the PI3K/AKT/mTOR cascade cannot be described as a mechanism universally capable of generating M2 macrophages. The outcomes depend on the protein involved, the AKT isoform, the intensity of the inhibition, the initial signal, and the cellular microenvironment.The most balanced interpretation is therefore that arctigenin reduced inflammatory markers and increased IL-10 and CD204 in the specific model studied. The definition of M2-like polarization is biologically

plausible but should not be automatically extended to all macrophage models or human clinical conditions.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the Evidence Review from independent research that confirms or defines the narrative of the paragraph.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cellular and animal	Peritoneal macrophages; mice with LPS-induced inflammation and TNBS-induced colitis	Reduction of IL-1b, IL-6, and TNF-a; increase in IL-10 and CD204; reduction of PI3K/AKT phosphorylation	direct confirmation	moderate
[1]	Cellular and animal	Macrophages; mice with DSS-induced colitis and alum-induced peritonitis	LZ205 reduced M1 characteristics and PI3K/AKT/mTOR signaling, with lower inflammation	direct confirmation	moderate
[2]	Cellular and animal	Macrophages and mice with LPS-induced sepsis	Exosomes with miR-150-5p reduced PI3K/AKT/mTOR, increased M2 markers, and attenuated inflammation	indirect confirmation	moderate
[3]	Cellular and animal	Murine macrophages and murine models of peritonitis and type 2 diabetes	Inhibition of PI3K-Akt2 reduced pro-inflammatory macrophage programs	biologically consistent evidence	moderate
[4]	Cellular and animal	Bone marrow-derived macrophages and murine model of sterile peritonitis	mTOR inhibition and loss of Lamtor1 reduced IL-4-induced M2 polarization	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed clearly supports that arctigenin, in the macrophages and mouse models examined, reduces pro-inflammatory mediators and the activation of the PI3K/AKT pathway, while simultaneously increasing IL-10 and CD204. Independent evidence makes the idea that selective modulation of this cascade can attenuate pro-inflammatory macrophage programs in specific models quite well-supported.The part regarding a true universal conversion from M1 to M2, however, requires validation. Macrophage polarization depends on the stimulus, metabolic conditions, and the molecular node involved. The evidence is therefore confirmed at a mechanistic level, without clinical proof of arctigenin in human inflammatory diseases.

Aggiornato al 25/11/2026. Questo contenuto riflette una sintesi divulgativa delle evidenze scientifiche al momento della pubblicazione e non sostituisce il parere medico.

10. TRANSPARENCY AND SCIENTIFIC RESPONSIBILITY

Artificial Intelligence was used solely as a tool for editorial and documentary support. All content, interpretations, bibliographic citations and conclusions have been verified, reviewed and approved by the author, who assumes full scientific responsibility for them.

The manuscript was also subjected to independent peer review prior to publication.

To ensure the greatest transparency, the complete history of the article, including the dates of submission, revision, acceptance and publication, as well as information on the peer review process, is available on the dedicated Article History page.

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